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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,646	08/15/2006	Erika Aina Zannou	33575-US-PCT	5086

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NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
WESTERBERG, NISSA M	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
02/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,646	ZANNOU ET AL.	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 - 27* is/are pending in the application.

4a) Of the above claim(s) *6, 7, 9, 13 - 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 - 5, 8, 10 - 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of group I and the inactive ingredient of D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS) in the reply filed on December 9, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112 – 1st Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection. None of the diseases related to irregular osteoclast activity other than hypercalcemia resulting from excessive

bone resorption secondary to hyperparathyroidism, thyrotoxicosis, sarcoidosis, or hypervitaminosis D meet the written description provision of 35 USC § 112, first paragraph, due to lacking information as to how related a condition must be to irregular osteoclast activity in order to meet this limitation. Many diseases may have at least some relationship to irregular osteoclast activity, and therefore this term encompass a myriad of diseases. The specification provides insufficient written description to support the full genus of disease related to irregular osteoclast activity and Applicant has not provided a description as to how much of a relationship a particular disease must have to irregular osteoclast activity in order to meet this limitation.

4. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating osteoporosis or diseases related to irregular osteoclast activity, does not reasonably provide enablement for the prevention of osteoporosis or diseases related to irregular osteoclast activity or treatment of all diseases related to irregular osteoclast activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The disclosure and claims of the application have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988) as to undue experimentation

The factors include:

1. The nature of the invention;
2. The breadth of the claims;

3. The predictability or unpredictability of the art;
4. The amount of direction or guidance presented;
5. The presence or absence of working examples
6. The quantity of experimentation necessary;
7. The state of the prior art; and
8. The relative skill of those skilled in the art.

Each factor is address below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

1. The nature of the invention, the breadth of the claims: The claims are directed towards a pharmaceutical formulation comprising a bisphosphonic acid or a salt thereof and an inactive ingredient with a hydrophilic-lipophilic balance (HLB) value of from about 1 to about 30 that is an ester of a medium chain fatty acid or a lipophilic polyethylene glycol ester. The bisphosphonic acid compound can be a bone resorption inhibitor with an intended use of treating or preventing osteoporosis or diseases related to irregular osteoclast activity.

2. The quantity of experimentation necessary, the state of the prior art, and the relative skill of those skilled in the art: The relative skill of those skilled in the art is high. The prior art recognizes that bisphosphonic acid compounds are useful for the treatment of disorders related to bone resorption and calcium metabolism such as

osteoporosis, Paget's disease or metastatic bone disease (US 6,468,559, col 1, ln 15 – 22). Various generations of these drugs have different properties. Etidronate is an example of compound with significant activity against these conditions but with the undesirable side effect of decrease bone mineralization. Other generations include drugs which reliably suppress bone resorption but cannot be administered orally or those compounds which are efficacious when administered either parenterally or orally (US '559, col 1, ln 22 – 27). To prevent is defined as to keep from happening or arising, make impossible (p 3, dictionary.com entry, accessed 11/27/08). The prior art recognizes that that drugs are useful for the treatment of osteoporosis and other disorders related to bone resorption. The prior art does not recognize that administration of these drugs are useful for the prevention of these conditions as individuals taking them can still develop these condition. The prior art also does not recognize that administration of these drugs will treat all diseases related to irregular osteoclast activity particularly in the case of certain drugs such as etidronate, the side effects can also lead to skeletal problems that could be related to irregular osteoclast activity.

Since the term "treating" is inclusive of various administrative timing schemes and thus provides adequate coverage for all reasonably successful therapies, the examiner recommends deleting the term "preventing" and simply reciting "treatment" only instead.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites the limitation "said bone resorption inhibitor" in line 2. There is insufficient antecedent basis for this limitation in the claim. This claim is also rejected because the meaning of the phrase “diseases related to irregular osteoclast activity” is indefinite. It is not defined whether any disease in which there is abnormal osteoclast activity in encompasses and/or what degree of association must be present for a particular disease to be related to irregular osteoclast activity. “Irregular osteoclast activity” could mean that the activity of the osteoclast varies over time and is not constant or it could mean that the activity of osteoclasts is abnormal and does not follow a variation in activity which is associated with normal osteoclast behavior.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1 – 4 and 10 – 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (US 6,468,559).

Chen et al. discloses pharmaceutical formulations of a bisphosphonic acid compound for the treatment of conditions associated with bone resorption such as osteoporeosis (abstract) and therefore the active ingredients are bone resorption inhibitors that is useful in the treatment of osteoporosis. The pharmaceutical formulation consists of a bisphosphonic acid or salt thereof in a pharmaceutically acceptable liquid or semi-solid carrier (col 6, ln 18 – 23), and the carrier can be a surfactant (col 9, ln 60 – 61). Suitable hydrophilic surfactants generally will have a HLB value greater than about 10 (col 13, ln 26 – 28). Example 1 (col 22, ln 19 – 42) has the bone resorption inhibitor alendronate and the ester of a medium chain fatty acid ester having a hydrophilic-lipophilic balance of from about 1 to about 30 of CAPMUL® MCM is prepared. For the treatment of Paget's disease, administration of 5mg/kg/day to 20 mg/kg/day of etidronate is indicated or for the treatment of tumor induced hypercalcemia, a dosage of 0.002 mg/kg to 0.04 mg/kg of zoledronate is indicated (col 21, ln 33 – 41).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1 – 5, 8 and 10 – 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6,468,559).

Chen et al. discloses pharmaceutical formulations of a bisphosphonic acid compound for the treatment of conditions associated with bone resorption such as

osteoporosis (abstract) and therefore the active ingredients are bone resorption inhibitors that is useful in the treatment of osteoporosis. The pharmaceutical formulation consists of a bisphosphonic acid or salt thereof in a pharmaceutically acceptable liquid or semi-solid carrier (col 6, ln 18 – 23), and the carrier can be a surfactant (col 9, ln 60 – 61). Suitable hydrophilic surfactants generally will have a HLB value greater than about 10 (col 13, ln 26 – 28). Example 1 (col 22, ln 19 – 42) has the bone resorption inhibitor alendronate and the ester of a medium chain fatty acid ester having a hydrophilic-lipophilic balance of from about 1 to about 30 of CAPMUL® MCM is prepared. Numerous other examples with other carriers with different HLB values are provided 9col 22, ln 45 – col 28, ln 39). For the treatment of Paget's disease, administration of 5mg/kg/day to 20 mg/kg/day of etidronate is indicated or for the treatment of tumor induced hypercalcemia, a dosage of 0.002 mg/kg to 0.04 mg/kg of zoledronate is indicated (col 21, ln 33 – 41).

Chen does not explicitly prepare an example with a bisphosphonic acid and D-alpha-tocopheryl polyethylene glycol 1000 (vitamin E TPGS).

Vitamin E TPGS is exemplified as a surfactant suitable for use as the carrier in the pharmaceutical formulation (col 14, ln 33 – 34).

It would have been obvious to one of ordinary skill in the art to prepare a pharmaceutical formulation comprising a bone resorption inhibitor such as alendronate or zoledronate and vitamin E TPGS as the carrier as Chen et al. discloses such compositions. One of ordinary skill would choose the best surfactant based on the cost and availability of the various carrier materials, and any potential interactions between

the various ingredients present in the pharmaceutical formulation. One of ordinary skill in the art would optimize the dosage of the active ingredient based upon a variety of factors such as the specific active ingredient chosen, the condition being treated, the severity of the condition in the patient and the dosing schedule of the medication as the amount of active ingredient present in the composition is a results effective parameter. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8 a.m. - 4 p.m. ET. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jake M. Vu/
Primary Examiner, Art Unit 1618

NMW